U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Salviati L, Trevisson E, Agosto C, et al. Primary Coenzyme Q_{10} Deficiency Overview. 2017 Jan 26 [Updated 2023 Jun 8]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Primary Coenzyme Q_{10} Deficiency Overview

Synonym: Primary Ubiquinone Deficiency

Leonardo Salviati, MD, PhD,[1] Eva Trevisson, MD, PhD,[1] Caterina Agosto, MD,[2] Mara Doimo, PhD,[1] and Placido Navas, PhD[3]

Created: January 26, 2017; Updated: June 8, 2023.

Summary

The following are the goals of this overview:

Goal 1

Briefly describe the clinical characteristics of primary coenzyme Q_{10} (CoQ_{10}) deficiency.

Goal 2

Increase the awareness of clinicians regarding genetic causes of primary CoQ_{10} deficiency.

Goal 3

Review the differential diagnosis of primary CoQ_{10} deficiency with a focus on genetic conditions.

Goal 4

Provide an evaluation strategy to identify the genetic cause of primary CoQ_{10} deficiency in a proband.

Goal 5

Review management of primary CoQ_{10} deficiency, including targeted pharmacologic treatment with high-dose oral CoQ_{10} supplementation and supportive treatment.

Goal 6

Inform genetic counseling of family members of an individual with primary CoQ_{10} deficiency.

Author Affiliations: 1 Clinical Genetics Unit, Department of Women and Children's Health, University of Padova, Padua, Italy; Email: leonardo.salviati@unipd.it; Email: eva.trevisson@unipd.it; Email: mara.doimo@unipd.it. 2 Pediatric Pain and Palliative Care Service, Department of Women's and Children's Health, Padua University Hospital, Padua, Italy; Email: caterina.agosto@aopd.veneto.it. 3 Centro Andaluz de Biología del Desarrollo, Universidad Pablo de Olavide, Sevilla, Spain; Email: pnavas@upo.es.

1. Clinical Characteristics of Primary Coenzyme Q_{10} Deficiency

Primary deficiency of coenzyme Q_{10} (CoQ_{10}), a lipid component of the mitochondrial respiratory chain, is classified as a mitochondrial respiratory chain disorder [DiMauro et al 2013]. In this *GeneReview*, the term "primary CoQ_{10} deficiency" refers to the group of conditions characterized by a reduction of CoQ_{10} levels in tissues or cultured cells associated with biallelic pathogenic variants in one of the ten genes involved in the biosynthesis of CoQ_{10}.

Primary CoQ_{10} deficiency (also referred to as primary ubiquinone deficiency) is associated with an extremely heterogeneous group of clinical manifestations, as described below (see also Table 1).

Clinical Manifestations

The manifestations of primary CoQ_{10} deficiency vary (see Table 1). Traditionally, clinical presentations have been classified into five distinct phenotypes: encephalomyopathy, cerebellar ataxia, severe infantile multisystem disease, steroid-resistant nephrotic syndrome, and isolated myopathy [Emmanuele et al 2012]. This classification is now outdated because the range of clinical phenotypes is much wider, and different combinations of findings with significant overlap have been identified. Furthermore, no individuals with molecularly confirmed primary CoQ_{10} deficiency with isolated myopathy have been reported [Authors, personal observation], since most individuals reported with predominantly muscle disease have secondary CoQ_{10} deficiency [Desbats et al 2015a] (see Differential Diagnosis).

The broad age of onset of primary CoQ_{10} deficiency is exemplified by *COQ2*-related CoQ_{10} deficiency, in which onset ranges from birth to the seventh decade.

The principal clinical manifestations of primary CoQ_{10} deficiency (regardless of genetic cause) are summarized below [Desbats et al 2015a], and followed by a summary of the phenotypes of *COQ2*-, *COQ8A*-, and *COQ8B*-related CoQ_{10} deficiencies, the four most common causes of primary CoQ_{10} deficiency.

Principal Clinical Manifestations

Neurologic. Central nervous system (CNS) manifestations include encephalopathy (a wide spectrum of brain involvement with different clinical and neuroradiologic features often not further specified). In some individuals encephalopathy is associated with findings on neuroimaging resembling Leigh syndrome [López et al 2006] or MELAS (with stroke-like episodes) [Salviati et al 2005]. CNS manifestations often include seizures, dystonia, spasticity, and/or intellectual disability [López et al 2006, Mollet et al 2007, Heeringa et al 2011].

The age of onset and clinical severity range from fatal neonatal encephalopathy with hypotonia [Mollet et al 2007, Jakobs et al 2013] to a late-onset, slowly progressive multiple system atrophy (MSA)-like phenotype, a neurodegenerative disorder characterized by autonomic failure associated with various combinations of parkinsonism, cerebellar ataxia, and pyramidal dysfunction. This clinical picture resembling MSA with onset in the seventh decade was reported in two multiplex families with *COQ2*-related CoQ_{10} deficiency [Mitsui et al 2013].

Individuals with *COQ8A*-related CoQ_{10} deficiency display progressive cerebellar atrophy and ataxia with intellectual disability and seizures [Lagier-Tourenne et al 2008, Mollet et al 2008]. Ataxia has also been reported in individuals with *COQ4*-related CoQ_{10} deficiency [Bosch et al 2018, Mero et al 2021, Cordts et al 2022].

Distal motor neuropathy has been reported in several individuals with *COQ7*-related CoQ_{10} deficiency [Jacquier et al 2023, Liu et al 2023]. Peripheral neuropathy has been reported in two sibs with *PDSS1*-related CoQ_{10} deficiency [Mollet et al 2007].

Given the small number of affected individuals described to date, clinical data are insufficient to make any generalizations about other neurologic manifestations (e.g., dystonia, spasticity, seizures, intellectual disability).

Renal. Steroid-resistant nephrotic syndrome (SRNS), an unusual feature of mitochondrial disorders, is a hallmark of primary CoQ_{10} deficiency. If not treated with supplementation of high-dose oral CoQ_{10} (see Management), SRNS usually progresses to end-stage kidney disease (ESKD). SRNS has been reported in association with variants in *PDSS1*, *PDSS2*, *COQ2*, *COQ6*, and *COQ8B* [Acosta et al 2016]. To date, SRNS has not been reported in association with variants in *COQ4*, *COQ8A*, and *COQ9* (including the mouse model).

Renal involvement usually manifests as proteinuria in infancy. Affected individuals often present initially with SRNS that leads to ESKD, followed by an encephalomyopathy with seizures and stroke-like episodes resulting in severe neurologic impairment and ultimately death [Rötig et al 2000, Salviati et al 2005, Heeringa et al 2011].

Some affected individuals manifest only SRNS with onset in the first or second decade of life and slow progression to ESKD without extrarenal manifestations [Gigante et al 2017].

One of the two individuals in a family with *COQ9*-related CoQ_{10} deficiency manifested tubulopathy within a few hours after birth.

Cardiac. Hypertrophic cardiomyopathy (HCM) has been reported in:

- Neonatal-onset *COQ2*-related CoQ_{10} deficiency [Scalais et al 2013];
- *COQ4*-related CoQ_{10} deficiency manifesting as prenatal-onset HCM [Brea-Calvo et al 2015];
- *COQ9*-related CoQ_{10} deficiency manifesting as neonatal-onset lactic acidosis followed by a multisystem disease that included HCM [Duncan et al 2009]. The cardiac disease worsened despite treatment with CoQ_{10}.

Ophthalmologic. Retinopathy, sometimes as an isolated manifestation in adults, has been reported in association with variants in *PDSS1*, *COQ2*, *COQ4*, and *COQ5* [Desbats et al 2016, Jurkute et al 2022].

Optic atrophy has been reported in some individuals with *PDSS1*-related CoQ_{10} deficiency [Mollet et al 2007], *PDSS2*-related CoQ_{10} deficiency [Rötig et al 2000], and *COQ2*-related CoQ_{10} deficiency [Stallworth et al 2023].

Sensorineural hearing loss, which is common in individuals with *COQ6*-related CoQ_{10} deficiency, is also observed in some individuals with *COQ2*-related CoQ_{10} [Drovandi et al 2022b] and *PDSS1*-related CoQ_{10} deficiency [Nardecchia et al 2021].

Muscle findings include weakness and exercise intolerance. Muscle biopsy may show nonspecific signs of lipid accumulation and mitochondrial proliferation [Trevisson et al 2011, Desbats et al 2015b]. Muscle involvement in primary CoQ_{10} deficiency is virtually always accompanied by extramuscular manifestations.

Prognosis. Data on the prognosis of primary CoQ_{10} deficiency are limited due to the small number of affected individuals reported to date. It is a progressive disorder, with variable rates of progression and tissue involvement depending on the gene involved and the severity of the CoQ_{10} deficiency.

Children with severe multisystem CoQ_{10} deficiency respond poorly to treatment and generally die within the neonatal period or in the first year of life.

Individuals with later-onset disease show better response to supplementation with high-dose oral CoQ_{10}. In many instances treatment can change the natural history of the disease by blocking progression of the kidney disease and preventing the onset of neurologic manifestations in persons with biallelic pathogenic variants in *COQ2*, *COQ6*, *COQ8B*, or *PDSS2* [Montini et al 2008; Heeringa et al 2011; Ashraf et al 2013; Authors, personal communication]. See Pharmacologic Treatment.

Phenotypes of *COQ2*-, *COQ8A*-, and *COQ8B*-Related Coenzyme Q_{10} Deficiencies

COQ2. The findings in affected individuals from the ten families described to date differ in severity and age of onset [Mollet et al 2007, Diomedi-Camassei et al 2007, Dinwiddie et al 2013, Jakobs et al 2013, McCarthy et al 2013, Mitsui et al 2013, Scalais et al 2013, Desbats et al 2015b, Desbats et al 2016].

The main clinical features include SRNS, which can be:

- Isolated [Diomedi-Camassei et al 2007, McCarthy et al 2013, Gigante et al 2017];
- Associated with encephalomyopathy [Salviati et al 2005] or severe multiple system disease [Diomedi-Camassei et al 2007, Mollet et al 2007, Jakobs et al 2013].

Adult-onset retinitis pigmentosa can be an isolated manifestation or can be associated with late-onset multiple system atrophy [Mitsui et al 2013, Desbats et al 2016].

COQ8A. Affected individuals experience onset of muscle weakness and reduced exercise tolerance between ages 18 months and three years, followed by cerebellar ataxia (the predominant clinical feature) with severe cerebellar atrophy on MRI. The disease course varies, including both progressive and apparently self-limited ataxia. The ataxia may be:

- Isolated [Lagier-Tourenne et al 2008];
- Progressive with cerebellar atrophy in addition to intellectual disability, epilepsy, stroke-like episodes, and/or exercise intolerance [Auré et al 2004, Lagier-Tourenne et al 2008, Mollet et al 2008, Terracciano et al 2012].

COQ8B. Affected individuals generally manifest SRNS in the first and second decade, and frequently evolve to end-stage kidney disease [Ashraf et al 2013, Korkmaz et al 2016]. In addition, four affected individuals were reported with mild intellectual disability, two with occasional seizures, and one with retinitis pigmentosa.

Laboratory Findings

Serum or plasma lactate concentration may be high in those individuals with severe neonatal onset. Of note, normal lactate levels do not exclude the possibility of primary CoQ_{10} deficiency [Rahman et al 2012].

Cerebrospinal fluid lactate concentration may be more sensitive than serum or plasma levels but can be normal.

2. Genetic Causes of Primary Coenzyme Q_{10} Deficiency

Table 1 lists the ten genes known to cause primary coenzyme Q_{10} (CoQ_{10}) deficiency. Note that while other genes are likely to cause primary CoQ_{10} deficiency, they have yet to be identified.

Table 1. Primary Coenzyme Q_{10} Deficiency: Genes and Associated Clinical Features

Gene [1]	# of Families w/CoQ_{10} Deficiency Attributed to Gene	Clinical Features					
		Kidneys	Heart	Eyes	Hearing	Neurologic	Muscles
COQ2	>10	SRNS	HCM	Retinopathy, optic atrophy	SNHL	Encephalopathy, [2] seizures, other [3]	Myopathy
COQ4	>10		Heart failure, HCM	Retinopathy		Encephalopathy, seizures, ataxia, other [4]	Myopathy

Table 1. continued from previous page.

Gene [1]	# of Families w/CoQ_{10} Deficiency Attributed to Gene	Clinical Features					
		Kidneys	Heart	Eyes	Hearing	Neurologic	Muscles
COQ5 [5]	2			Retinopathy			
COQ6	>10	SRNS [6]			SNHL	Encephalopathy, seizures	
COQ7	>10					Encephalopathy, ID, peripheral neuropathy	Muscle weakness
COQ8A	>10					Encephalopathy, cerebellar ataxia (SCAR9), [7] dystonia, spasticity, seizures	Exercise intolerance
COQ8B	>10	SRNS [6]				ID, seizures	
COQ9	2	Tubulopathy	HCM			Encephalopathy	Myopathy
PDSS1	10	SRNS		Retinopathy, optic atrophy		Encephalopathy, peripheral neuropathy, ataxia	
PDSS2	3	SRNS		Retinopathy	SNHL	Leigh syndrome, ataxia	

HCM = hypertrophic cardiomyopathy; ID = intellectual disability; SNHL = sensorineural hearing loss; SRNS = steroid-resistant nephrotic syndrome

1. Genes are listed in alphanumeric order.

2. Encephalopathy comprises a wide spectrum of brain involvement with different clinical and neuroradiologic features, often not further explained by the reporting authors.

3. Adult-onset multisystem atrophy-like phenotype [Desbats et al 2016]

4. Severe hypotonia, respiratory insufficiency, cerebellar hypoplasia, slowly progressive neurologic deterioration, spasticity, and intellectual disability

5. The link between *COQ5* pathogenic variants and ataxia still needs confirmation.

6. Because individuals with *COQ6*- and *COQ8B*-related CoQ_{10} deficiency were ascertained by the presence of SRNS, the authors cannot exclude the possibility that biallelic pathogenic variants in these two genes could also cause a broader phenotype.

7. *COQ8A*-related CoQ_{10} deficiency is also referred to as autosomal recessive spinocerebellar ataxia 9 or SCAR9 (OMIM 612016).

3. Differential Diagnosis of Primary Coenzyme Q_{10} Deficiency

Note: It is important to consider primary coenzyme Q_{10} (CoQ_{10}) deficiency in individuals with the following diverse presentations because primary CoQ_{10} deficiency is potentially treatable by supplementation with high-dose oral CoQ_{10}:

- **Mitochondrial encephalomyopathies.** The clinical manifestations of mitochondrial encephalomyopathies and primary CoQ_{10} deficiency can often be indistinguishable, especially in the severe phenotypes. See Primary Mitochondrial Disorders Overview.
- **Steroid-resistant nephrotic syndrome (SRNS)** that results from pathogenic variants in other genes important for podocyte function and is clinically indistinguishable from the SRNS resulting from primary CoQ_{10} deficiency. See Genetic Steroid-Resistant Nephrotic Syndrome Overview.
- **Early-onset ataxia.** See Hereditary Ataxia Overview.
- **Retinitis pigmentosa** and **optic atrophy.** See Nonsyndromic Retinitis Pigmentosa Overview.

Secondary CoQ_{10} deficiencies are disorders in which reduction in CoQ_{10} levels are caused by pathogenic variants in genes not directly related to CoQ_{10} biosynthesis [Trevisson et al 2011]. Molecular genetic testing is

the only way to distinguish primary CoQ_{10} deficiency from the secondary CoQ_{10} deficiencies. Some causes of secondary CoQ_{10} deficiency are respiratory chain defects (see Primary Mitochondrial Disorders Overview), multiple acyl-CoA dehydrogenase deficiency, and ataxia with oculomotor apraxia type 1 (OMIM 208920).

4. Evaluation Strategies to Identify the Genetic Cause of Primary Coenzyme Q_{10} Deficiency in a Proband

Establishing a specific genetic cause of primary coenzyme Q_{10} (CoQ_{10}) deficiency:

- Allows initiation of a specific treatment;
- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, laboratory testing, family history, and genomic/genetic testing.

Medical history. Primary CoQ_{10} deficiency should be suspected in all individuals with any of the clinical (and neuroradiologic) manifestations suggestive of a mitochondrial encephalomyopathy, with steroid-resistant nephrotic syndrome (especially when other neurologic manifestations are present), retinitis pigmentosa, and/or unexplained ataxia. It should also be considered in individuals with motor neuropathy without other clear causes.

Physical examination. There are no pathognomonic clinical signs for primary CoQ_{10} deficiency. A standard physical examination as well as a neurologic examination should be performed in all individuals.

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

The diagnosis of primary CoQ_{10} deficiency is usually established by molecular genetic testing; however, biochemical testing can be helpful in some circumstances.

Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

A multigene panel (such as for steroid-resistant nephrotic syndrome, mitochondrial disorders of nuclear origin, retinitis pigmentosa, ataxia, or peripheral neuropathy) that includes the ten genes in Table 1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. Exome sequencing is most commonly used; genome sequencing is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Biochemical Testing

In the past, biochemical testing was the primary method for diagnosing CoQ_{10} deficiency; however, currently its use is limited to either establishing the diagnosis when it cannot be established by molecular genetic testing or confirming molecular genetic testing results (such as variants of uncertain significance). The following findings on biochemical testing can differentiate CoQ_{10} deficiency from other mitochondrial disorders with similar clinical findings, but cannot differentiate primary from secondary CoQ_{10} deficiency (see Differential Diagnosis).

- Reduced levels of CoQ_{10} in skeletal muscle [Montero et al 2008]

  Note: While CoQ_{10} measurements may be performed on cultured skin fibroblasts or blood mononuclear cells, these tissues may not be reliable in detecting secondary CoQ_{10} defects [Yubero et al 2015].

- Reduced activities of complex I+III and II+III of the mitochondrial respiratory chain on frozen muscle homogenates

  These enzymatic activities, which depend on endogenous CoQ_{10}, are reduced in individuals with a defect in CoQ_{10} even when isolated complex II and III respiratory chain activities are normal [Rahman et al 2012].

Plasma CoQ_{10} levels are not useful for the diagnosis of primary CoQ_{10} deficiency because they reflect dietary intake rather than endogenous CoQ_{10} production [Trevisson et al 2011]. Moreover, there are individuals with genetically proven CoQ_{10} deficiency who had normal CoQ_{10} levels in both muscle and cultured skin fibroblasts [Mero et al 2021]; therefore, a normal result does not rule out the diagnosis. For these reasons, and due to the scarcity of laboratories that can perform CoQ_{10} measurements in tissues on a routine basis, biochemical testing has been largely abandoned as a first-line diagnostic tool.

5. Management

No clinical practice guidelines for management of primary coenzyme Q_{10} (CoQ_{10}) deficiency have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with primary CoQ_{10} deficiency, the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 2. Primary Coenzyme Q_{10} Deficiency: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Encephalopathy	• Assessment of functional neurologic status by pediatric neurologist • Brain MRI	Check for neuroradiologic signs of Leigh syndrome or MELAS.

Table 2. continued from previous page.

System/Concern	Evaluation	Comment
Adult-onset neurologic complications	Assess for evidence of autonomic dysfunction & movement disorders (parkinsonism, cerebellar ataxia, pyramidal signs).	
Neuromuscular	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Need for durable medical equipment &/or adaptive devices
	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Intellectual disability	Eval for educational placement	
Seizures	EEG	
Peripheral neuropathy	Assess muscle strength & reflexes, & exercise tolerance.	Consider performing EMG & nerve conduction studies in persons w/*COQ7*-related CoQ_{10} deficiency
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval for gastrointestinal dysmotility, aspiration risk, & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.
Hearing loss	Audiometry w/particular attention to possible SNHL	
Retinopathy	Ophthalmologic eval & electroretinogram in all persons	Particular attention to: • Possible retinopathy & optic atrophy • Possible need for low vision services
Cardiac	Cardiac eval	Incl echocardiography w/particular attention to possible HCM
Steroid-resistant nephrotic syndrome	Renal eval w/particular attention to presence of proteinuria, kidney function	
Ethics consultation	Clinical ethics services	Assess health care decisions in context of best interest of child & values & preferences of family
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of primary CoQ_{10} deficiency to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

HCM = hypertrophic cardiomyopathy; MOI = mode of inheritance; SNHL = sensorineural hearing loss

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for primary CoQ_{10} deficiency.

Pharmacologic Treatment

Coenzyme Q_{10} supplementation. Individuals with primary CoQ_{10} deficiency may respond well to high-dose oral CoQ_{10} supplementation (ranging from 5 to 50 mg/kg/day). Soluble formulations are apparently more bioavailable [Desbats et al 2015a].

Treatment should be instituted as early as possible because it can limit disease progression and reverse some manifestations [Montini et al 2008]; however, established severe neurologic and/or renal damage cannot be reversed.

Response is highly variable, and depends on both the specific genetic defect and disease severity, but also other unknown factors.

- ***COQ2*-related CoQ_{10} deficiency.** Response was poor in individuals with severe forms with onset in the first months of life, while both neurologic manifestations and SRNS responded well to CoQ_{10} supplementation in individuals with later-onset disease. The response apparently correlates with severity of the *COQ2* variants [Desbats et al 2016].
- ***COQ4*-related CoQ_{10} deficiency.** No response was observed in individuals reported by Chung et al [2015] and in five individuals reported by Yu et al [2019]. Partial response was seen in one of the two individuals with ataxia reported by Mero et al [2021], in the individual reported by Caglayan et al [2019], and in four individuals reported by Yu et al [2019]. Among the individuals reported by Yu et al [2019], those who did not respond to treatment had one null variant, while those who responded to supplementation with high-dose oral CoQ_{10} had two missense variants.
- ***COQ6*-related CoQ_{10} deficiency.** Homozygotes for the pathogenic variants p.Gly255Arg or p.Ala353Asp responded well [Heeringa et al 2011].
- ***COQ8B*-related CoQ_{10} deficiency.** An individual homozygous for a truncating pathogenic variant responded to supplementation with high-dose oral CoQ_{10} with resolution of edema and significant improvement of proteinuria [Ashraf et al 2013].
- ***PDSS2*-related CoQ_{10} deficiency.** Individuals with severe neonatal-onset disease responded poorly to supplementation with high-dose oral CoQ_{10} supplementation, whereas those with later-onset disease responded better [Rötig et al 2000; Authors, personal observation]. Of note, CoQ_{10} supplementation is effective in the mouse model of *PDSS2*-related CoQ_{10} deficiency.
- ***COQ8A*-related CoQ_{10} deficiency.** While most affected individuals respond poorly to high-dose oral CoQ_{10} supplementation, three individuals had a favorable response: one had objective stabilization of ataxia [Lagier-Tourenne et al 2008]; one had a dramatic and long-lasting improvement of dystonia and myoclonus after six months of treatment; and one individual's tremor and drawing ability improved [Mignot et al 2013].

A recent study that investigated the effect of supplementation with high-dose oral CoQ_{10} on renal manifestations [Drovandi et al 2022a] reported that the best response was observed in individuals with *COQ6*-related CoQ_{10} deficiency.

Data for response to high-dose oral CoQ_{10} supplementation in individuals with primary CoQ_{10} deficiency caused by variants in other genes are limited or lacking.

Ineffective treatments or those without validated effects for individuals with primary CoQ_{10} deficiency include the following CoQ_{10} derivatives:

- Ubiquinol, the reduced form of CoQ_{10}. Although this has recently become commercially available, data on the therapeutic dosage and its efficacy are still lacking.
- Short-chain quinone analogs such as idebenone [Rötig et al 2000, López et al 2010] have been reported to cause clinical deterioration in individuals with CoQ_{10} deficiency [Hargreaves 2014].
- Bypass therapy with analogs of the quinone ring [Pesini et la 2022] and the use of capsofungin to improve bioavailability of CoQ_{10} [Wang & Hekimi 2020] have been tested in cellular models and in mice, but no data are available in humans.

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 3).

Table 3. Primary Coenzyme Q_{10} Deficiency: Treatment of Manifestations by Phenotype

Manifestation/Concern	Treatment	Considerations/Other
Fatal Neonatal Encephalopathy Phenotype		
Nutrition/Feeding	By feeding team incl nutritionist, gastroenterologist	Nasogastric tube, gastrostomy tube
Steroid-resistant nephrotic syndrome	Per treating nephrologist	• See Steroid-Resistant Nephrotic Syndrome Overview, Management. • ACE inhibitors may be used in combination w/CoQ_{10} supplementation in persons w/ proteinuria. [1] • Kidney transplantation is an option for those w/ESKD. [2]
Respiratory insufficiency	Per treating pulmonologist	May incl consideration of tracheostomy & artificial ventilation
Neuromuscular	Physical therapy	• To maintain muscle strength & mobility & prevent contractures • Consider need for adaptive positioning devices.
Seizures	Standard treatment w/ASM by experienced neurologist based on seizure semiology	• Certain ASMs require monitoring of medication levels. • Education of parents/caregivers [3]
Sensorineural hearing loss	By hearing loss specialists	See Genetic Hearing Loss Overview.
Cardiomyopathy	Per standard treatment protocols	
Retinopathy	Per treating ophthalmologist & low vision services	
Other Neurologic Phenotypes		
Peripheral neuropathy	See Charcot-Marie-Tooth Hereditary Neuropathy Overview.	
Cerebellar ataxia	See Hereditary Ataxia Overview.	

Table 3. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Dystonia	According to standard care	
Spasticity		

ASM = anti-seizure medication
1. Heeringa et al [2011]
2. Salviati et al [2005]
3. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

While monitoring the existing manifestations of primary CoQ_{10} deficiency, the individual's response to pharmacologic treatment and supportive care, and the emergence of new manifestations depends on the specific genetic cause and on the individual's clinical manifestations, it should always include periodic evaluations of the following:

- In individuals with adult-onset neurologic findings and individuals with apparently isolated SRNS: assessment for evidence of autonomic dysfunction and movement disorders (parkinsonism, cerebellar ataxia, pyramidal signs) every one to two years
- Urine analysis for proteinuria and assessment of kidney function
- Ophthalmologic evaluation and electroretinogram for evidence of retinopathy and to determine need for low vison services
- Hearing evaluation with attention to possible sensorineural hearing loss

Note: Because cardiomyopathy to date has been found only in the most severe phenotype (i.e., neonatal onset), cardiac evaluation should be performed at the time of diagnosis but not periodically unless cardiac involvement has been documented.

Evaluation of Relatives at Risk

Given the importance of early CoQ_{10} supplementation in persons with primary CoQ_{10} deficiency, it is appropriate to evaluate the sibs of a proband who has primary CoQ_{10} deficiency in order to identify as early as possible those sibs who would benefit from early initiation of treatment (see Pharmacologic Treatment).

- If the pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known and the diagnosis has been established by biochemical findings, one can consider measuring CoQ_{10} levels in skin fibroblasts of at-risk sibs [Desbats et al 2015b].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

6. Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Primary coenzyme Q_{10} (CoQ_{10}) deficiency is generally inherited in an autosomal recessive manner.

Primary CoQ_{10} deficiency associated with a *de novo* contiguous gene deletion encompassing *COQ4* was reported in one individual [Salviati et al 2012].

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The parents of an individual with a confirmed molecular genetic diagnosis of primary CoQ_{10} deficiency are presumed to be heterozygous for a *COQ2*, *COQ4*, *COQ5*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B*, *COQ9*, *PDSS1*, or *PDSS2* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a primary CoQ_{10} deficiency-related pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a primary CoQ_{10} deficiency-related pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with a confirmed molecular genetic diagnosis of primary CoQ_{10} deficiency are obligate heterozygotes (i.e., carriers) for a primary CoQ_{10} deficiency-related pathogenic variant.

Other family members. Each sib of the parents of a proband with a confirmed molecular genetic diagnosis of primary CoQ_{10} deficiency is at a 50% risk of being a carrier of a primary CoQ_{10} deficiency-related pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the primary CoQ_{10} deficiency-related pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the primary CoQ_{10} deficiency-related pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for primary CoQ_{10} deficiency are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Primary coenzyme Q10 deficiency

Chapter Notes

Author Notes

Leonardo Salviati (leonardo.salviati@unipd.it) and Eva Trevisson (eva.trevisson@unipd.it) are actively involved in clinical research regarding individuals with primary CoQ_{10} deficiency. They would be happy to communicate with persons who have any questions regarding diagnosis of primary CoQ_{10} deficiency or other considerations.

Leonardo Salviati and Eva Trevisson are also interested in hearing from clinicians treating families affected by primary CoQ_{10} deficiency in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Drs Salviati and Trevisson to inquire about review of variants of uncertain significance in any of the genes listed in Table 1.

Acknowledgments

This work is supported by Telethon Italy Grants GGP13222 and GGP14187, a grant from Fondazione CARIPARO, and University of Padova Grant CPDA123573/12 (to LS); Ministry of Health Grant GR-2009-1578914 (to ET); and grants from Fondazione IRP Città della Speranza (to LS and ET).

Author History

Caterina Agosto, MD (2023-present)
Mara Doimo, PhD (2017-present)
Leonardo Salviati, MD, PhD (2017-present)
Eva Trevisson, MD, PhD (2017-present)
Placido Navas, PhD (2017-present)

Revision History

- 8 June 2023 (bp) Comprehensive update posted live; scope changed to overview
- 26 January 2017 (bp) Review posted live
- 20 February 2015 (ls) Original submission

References

Literature Cited

Acosta MJ, Vazquez Fonseca L, Desbats MA, Cerqua C, Zordan R, Trevisson E, Salviati L. Coenzyme Q biosynthesis in health and disease. Biochim Biophys Acta. 2016;1857:1079-85. PubMed PMID: 27060254.

Ashraf S, Gee HY, Woerner S, Xie LX, Vega-Warner V, Lovric S, Fang H, Song X, Cattran DC, Avila-Casado C, Paterson AD, Nitschké P, Bole-Feysot C, Cochat P, Esteve-Rudd J, Haberberger B, Allen SJ, Zhou W, Airik R, Otto EA, Barua M, Al-Hamed MH, Kari JA, Evans J, Bierzynska A, Saleem MA, Böckenhauer D, Kleta R, El Desoky S, Hacihamdioglu DO, Gok F, Washburn J, Wiggins RC, Choi M, Lifton RP, Levy S, Han Z, Salviati L, Prokisch H, Williams DS, Pollak M, Clarke CF, Pei Y, Antignac C, Hildebrandt F. ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10 biosynthesis disruption. J Clin Invest. 2013;123:5179-89. PubMed PMID: 24270420.

Auré K, Benoist JF, Ogier de Baulny H, Romero NB, Rigal O, Lombes A. Progression despite replacement of a myopathic form of coenzyme Q10 defect. Neurology. 2004;63:727-9. PubMed PMID: 15326254.

Bosch AM, Kamsteeg EJ, Rodenburg RJ, van Deutekom AW, Buis DR, Engelen M, Cobben JM. Coenzyme Q10 deficiency due to a COQ4 gene defect causes childhood-onset spinocerebellar ataxia and stroke-like episodes. Mol Genet Metab Rep. 2018;17:19-21. PubMed PMID: 30225196.

Brea-Calvo G, Haack TB, Karall D, Ohtake A, Invernizzi F, Carrozzo R, Kremer L, Dusi S, Fauth C, Scholl-Bürgi S, Graf E, Ahting U, Resta N, Laforgia N,Verrigni D, Okazaki Y, Kohda M, Martinelli D, Freisinger P, Strom TM, Meitinger T, Lamperti C, Lacson A, Navas P, Mayr JA, Bertini E, Murayama K, Zeviani M, Prokisch H, Ghezzi D. COQ4 mutations cause a broad spectrum of mitochondrial disorders associated with CoQ10 deficiency. Am J Hum Genet. 2015; 96:309-17. PubMed PMID: 25658047.

Caglayan AO, Gumus H, Sandford E, Kubisiak TL, Ma Q, Ozel AB, Per H, Li JZ, Shakkottai VG, Burmeister M. COQ4 mutation leads to childhood-onset ataxia improved by CoQ10 administration. Cerebellum. 2019;18:665-9. PubMed PMID: 30847826.

Chung WK, Martin K, Jalas C, Braddock SR, Juusola J, Monaghan KG, Warner B, Franks S, Yudkoff M, Lulis L, Rhodes RH, Prasad V, Torti E, Cho MT, Shinawi M. Mutations in COQ4, an essential component of coenzyme Q biosynthesis, cause lethal neonatal mitochondrial encephalomyopathy. J Med Genet. 2015;52:627-35. PubMed PMID: 26185144.

Cordts I, Semmler L, Prasuhn J, Seibt A, Herebian D, Navaratnarajah T, Park J, Deininger N, Laugwitz L, Göricke SL, Lingor P, Brüggemann N, Münchau A, Synofzik M, Timmann D, Mayr JA, Haack TB, Distelmaier F, Deschauer M. Bi-allelic COQ4 variants cause adult-onset ataxia-spasticity spectrum disease. Mov Disord. 2022;37:2147-53. PubMed PMID: 36047608.

Desbats MA, Lunardi G, Doimo M, Trevisson E, Salviati L. Genetic bases and clinical manifestations of coenzyme Q10 (CoQ 10) deficiency. J Inherit Metab Dis. 2015a;38:145-56. PubMed PMID: 25091424.

Desbats MA, Morbidoni V, Silic-Benussi M, Doimo M, Ciminale V, Cassina M, Sacconi S, Hirano M, Basso G, Pierrel F, Navas P, Salviati L, Trevisson E. The COQ2 genotype predicts the severity of coenzyme Q10 deficiency. Hum Mol Genet. 2016;25:4256-65. PubMed PMID: 27493029.

Desbats MA, Vetro A, Limongelli I, Lunardi G, Casarin A, Doimo M, Spinazzi M, Angelini C, Cenacchi G, Burlina A, Rodriguez Hernandez MA, Chiandetti L, Clementi M, Trevisson E, Navas P, Zuffardi O, Salviati L. Primary coenzyme Q(10) deficiency presenting as fatal neonatal multiorgan failure. Eur J Hum Genet. 2015b;23:1254-8. PubMed PMID: 25564041.

DiMauro S, Schon EA, Carelli V, Hirano M. The clinical maze of mitochondrial neurology. Nat Rev Neurol. 2013;9:429-44. PubMed PMID: 23835535.

Dinwiddie DL, Smith LD, Miller NA, Atherton AM, Farrow EG, Strenk ME, Soden SE, Saunders CJ, Kingsmore SF. Diagnosis of mitochondrial disorders by concomitant next-generation sequencing of the exome and mitochondrial genome. Genomics. 2013;102:148-56. PubMed PMID: 23631824.

Diomedi-Camassei F, Di Giandomenico S, Santorelli FM, Caridi G, Piemonte F, Montini G, Ghiggeri GM, Murer L, Barisoni L, Pastore A, Muda AO, Valente ML, Bertini E, Emma F. COQ2 nephropathy: a newly described inherited mitochondriopathy with primary renal involvement. J Am Soc Nephrol. 2007;18:2773-80. PubMed PMID: 17855635.

Drovandi S, Lipska-Ziętkiewicz BS, Ozaltin F, Emma F, Gulhan B, Boyer O, Trautmann A, Xu H, Shen Q, Rao J, Riedhammer KM, Heemann U, Hoefele J, Stenton SL, Tsygin AN, Ng KH, Fomina S, Benetti E, Aurelle M, Prikhodina L, Schreuder MF, Tabatabaeifar M, Jankowski M, Baiko S, Mao J, Feng C, Liu C, Sun S, Deng F, Wang X, Clavé S, Stańczyk M, Bałasz-Chmielewska I, Fila M, Durkan AM, Levart TK, Dursun I, Esfandiar N, Haas D, Bjerre A, Anarat A, Benz MR, Talebi S, Hooman N, Ariceta G, Schaefer F, et al. Oral coenzyme Q10 supplementation leads to better preservation of kidney function in steroid-resistant nephrotic syndrome due to primary coenzyme Q10 deficiency. Kidney Int. 2022a;102:604-12. PubMed PMID: 35643375.

Drovandi S, Lipska-Ziętkiewicz BS, Ozaltin F, Emma F, Gulhan B, Boyer O, Trautmann A, Ziętkiewicz S, Xu H, Shen Q, Rao J, Riedhammer KM, Heemann U, Hoefele J, Stenton SL, Tsygin AN, Ng KH, Fomina S, Benetti E, Aurelle M, Prikhodina L, Schijvens AM, Tabatabaeifar M, Jankowski M, Baiko S, Mao J, Feng C, Deng F, Rousset-Rouviere C, Stańczyk M, Bałasz-Chmielewska I, Fila M, Durkan AM, Levart TK, Dursun I, Esfandiar N, Haas D, Bjerre A, Anarat A, Benz MR, Talebi S, Hooman N, Ariceta G, Schaefer F, et al. Variation of the clinical spectrum and genotype-phenotype associations in coenzyme Q10 deficiency associated glomerulopathy. Kidney Int. 2022b;102:592-603. PubMed PMID: 35483523.

Duncan AJ, Bitner-Glindzicz M, Meunier B, Costello H, Hargreaves IP, López LC, Hirano M, Quinzii CM, Sadowski MI, Hardy J, Singleton A, Clayton PT, Rahman S. A nonsense mutation in COQ9 causes autosomal-recessive neonatal-onset primary coenzyme Q10 deficiency: a potentially treatable form of mitochondrial disease. Am J Hum Genet. 2009;84:558-66. PubMed PMID: 19375058.

Emmanuele V, López LC, Berardo A, Naini A, Tadesse S, Wen B, D'Agostino E, Solomon M, DiMauro S, Quinzii C, Hirano M. Heterogeneity of coenzyme Q10 deficiency: patient study and literature review. Arch Neurol. 2012; 69:978-83. PubMed PMID: 22490322.

Gigante M, Diella S, Santangelo L, Trevisson E, Acosta MJ, Amatruda M, Finzi G, Caridi G, Murer L, Accetturo M, Ranieri E, Ghiggeri GM, Giordano M, Grandaliano G, Salviati L, Gesualdo L. Further phenotypic heterogeneity of CoQ10 deficiency associated with steroid resistant nephrotic syndrome and novel COQ2 and COQ6 variants. Clin Genet. 2017;92:224-6. PubMed PMID: 28044327.

Hargreaves IP. Coenzyme Q10 as a therapy for mitochondrial disease. Int J Biochem Cell Biol. 2014;49:105-11. PubMed PMID: 24495877.

Heeringa SF, Chernin G, Chaki M, Zhou W, Sloan AJ, Ji Z, Xie LX, Salviati L, Hurd TW, Vega-Warner V, Killen PD, Raphael Y, Ashraf S, Ovunc B, Schoeb DS, McLaughlin HM, Airik R, Vlangos CN, Gbadegesin R, Hinkes B, Saisawat P, Trevisson E, Doimo M, Casarin A, Pertegato V, Giorgi G, Prokisch H, Rötig A, Nürnberg G, Becker C, Wang S, Ozaltin F, Topaloglu R, Bakkaloglu A, Bakkaloglu SA, Müller D, Beissert A, Mir S, Berdeli A, Varpizen S, Zenker M, Matejas V, Santos-Ocaña C, Navas P, Kusakabe T, Kispert A, Akman S, Soliman NA, Krick S, Mundel P, Reiser J, Nürnberg P, Clarke CF, Wiggins RC, Faul C, Hildebrandt F. COQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. J Clin Invest. 2011;121:2013-24. PubMed PMID: 21540551.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Jacquier A, Theuriet J, Fontaine F, Mosbach V, Lacoste N, Ribault S, Risson V, Carras J, Coudert L, Simonet T, Latour P, Stojkovic T, Piard J, Cosson A, Lesca G, Bouhour F, Allouche S, Puccio H, Pégat A, Schaeffer L.

Homozygous COQ7 mutation: a new cause of potentially treatable distal hereditary motor neuropathy. Brain. 2023;146:3470-83. PubMed PMID: 36454683.

Jakobs BS, van den Heuvel LP, Smeets RJ, de Vries MC, Hien S, Schaible T, Smeitink JA, Wevers RA, Wortmann SB, Rodenburg RJ. A novel mutation in COQ2 leading to fatal infantile multisystem disease. J Neurol Sci. 2013;326:24-8. PubMed PMID: 23343605.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Jurkute N, Cancellieri F, Pohl L, Li CHZ, Heaton RA, Reurink J, Bellingham J, Quinodoz M, Yioti G, Stefaniotou M, Weener M, Zuleger T, Haack TB, Stingl K; Genomics England Research Consortium; Hoyng CB, Mahroo OA, Hargreaves I, Raymond FL, Michaelides M, Rivolta C, Kohl S, Roosing S, Webster AR, Arno G. Biallelic variants in coenzyme Q10 biosynthesis pathway genes cause a retinitis pigmentosa phenotype. NPJ Genom Med. 2022;7:60. PubMed PMID: 36266294.

Korkmaz E, Lipska-Ziętkiewicz BS, Boyer O, Gribouval O, Fourrage C, Tabatabaei M, Schnaidt S, Gucer S, Kaymaz F, Arici M, Dinckan A, Mir S, Bayazit AK, Emre S, Balat A, Rees L, Shroff R, Bergmann C, Mourani C, Antignac C, Ozaltin F, Schaefer F, et al. ADCK4-associated glomerulopathy causes adolescence-onset FSGS. J Am Soc Nephrol. 2016;27:63-8. PubMed PMID: 25967120.

Lagier-Tourenne C, Tazir M, López LC, Quinzii CM, Assoum M, Drouot N, Busso C, Makri S, Ali-Pacha L, Benhassine T, Anheim M, Lynch DR, Thibault C, Plewniak F, Bianchetti L, Tranchant C, Poch O, DiMauro S, Mandel JL, Barros MH, Hirano M, Koenig M. ADCK3, an ancestral kinase, is mutated in a form of recessive ataxia associated with coenzyme Q10 deficiency. Am J Hum Genet. 2008;82:661-72. PubMed PMID: 18319074.

Liu XX, Wang N, Chen YK, Lv WQ, Hong JM, Xu GR, Zhou LY, Chen WJ, Fan DS, He J. Biallelic variants in the COQ7 gene cause distal hereditary motor neuropathy in two Chinese families. Brain. 2023;146:e27-e30. PubMed PMID: 36758993.

López LC, Quinzii CM, Area E, Naini A, Rahman S, Schuelke M, Salviati L, Dimauro S, Hirano M. Treatment of CoQ(10) deficient fibroblasts with ubiquinone, CoQ analogs, and vitamin C: time- and compound-dependent effects. PLoS One. 2010;5:e11897. PubMed PMID: 20689595.

López LC, Schuelke M, Quinzii CM, Kanki T, Rodenburg RJ, Naini A, Dimauro S, Hirano M. Leigh syndrome with nephropathy and CoQ10 deficiency due to decaprenyl diphosphate synthase subunit 2 (PDSS2) mutations. Am J Hum Genet. 2006;79:1125-9. PubMed PMID: 17186472.

McCarthy HJ, Bierzynska A, Wherlock M, Ognjanovic M, Kerecuk L, Hegde S, Feather S, Gilbert RD, Krischock L, Jones C, Sinha MD, Webb NJ, Christian M, Williams MM, Marks S, Koziell A, Welsh GI, Saleem MA, et al. Simultaneous sequencing of 24 genes associated with steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2013;8:637-48. PubMed PMID: 23349334.

Mero S, Salviati L, Leuzzi V, Rubegni A, Calderan C, Nardecchia F, Galatolo D, Desbats MA, Naef V, Gemignani F, Novelli M, Tessa A, Battini R, Santorelli FM, Marchese M. New pathogenic variants in COQ4 cause ataxia and neurodevelopmental disorder without detectable CoQ10 deficiency in muscle or skin fibroblasts. J Neurol. 2021;268:3381-9. PubMed PMID: 33704555.

Mignot C, Apartis E, Durr A, Marques Lourenço C, Charles P, Devos D, Moreau C, de Lonlay P, Drouot N, Burglen L, Kempf N, Nourisson E, Chantot-Bastaraud S, Lebre AS, Rio M, Chaix Y, Bieth E, Roze E, Bonnet I, Canaple S, Rastel C, Brice A, Rötig A, Desguerre I, Tranchant C, Koenig M, Anheim M. Phenotypic variability in ARCA2 and identification of a core ataxic phenotype with slow progression. Orphanet J Rare Dis. 2013;8:173. PubMed PMID: 24164873.

Mitsui J, Matsukawa T, Ishiura H, Fukuda Y, Ichikawa Y, Date H, Ahsan B, Nakahara Y, Momose Y, Takahashi Y, Iwata A, Goto J, Yamamoto Y, Komata M, Shirahige K, Hara K, Kakita A, Yamada M, Takahashi H, Onodera O, Nishizawa M, Takashima H, Kuwano R, Watanabe H, Ito M, Sobue G, Soma H, Yabe I, Sasaki H, Aoki M, Ishikawa K, Mizusawa H, Kanai K, Hattori T, Kuwabara S, Arai K, Koyano S, Kuroiwa Y, Hasegawa K, Yuasa T, Yasui K, Nakashima K, Ito H, Izumi Y, Kaji R, Kato T, Kusunoki S, Osaki Y, Horiuchi M, Kondo T, Murayama S, Hattori N, Yamamoto M, Murata M, Satake W, Toda T, Dürr A, Brice A, Filla A, Klockgether T, Wüllner U, Nicholson G, Gilman S, Shults CW, Tanner CM, Kukull WA, Lee VM, Masliah E, Low PA, Sandroni P, Trojanowski JQ, Ozelius L, Foroud T, Tsuji S. Mutations in COQ2 in familial and sporadic multiple-system atrophy. N Engl J Med. 2013;369:233-44. PubMed PMID: 23758206.

Mollet J, Delahodde A, Serre V, Chretien D, Schlemmer D, Lombes A, Boddaert N, Desguerre I, de Lonlay P, de Baulny HO, Munnich A, Rötig A. CABC1 gene mutations cause ubiquinone deficiency with cerebellar ataxia and seizures. Am J Hum Genet. 2008;82:623-30. PubMed PMID: 18319072.

Mollet J, Giurgea I, Schlemmer D, Dallner G, Chretien D, Delahodde A, Bacq D, de Lonlay P, Munnich A, Rötig A. Prenyldiphosphate synthase, subunit 1 (PDSS1) and OH-benzoate polyprenyltransferase (COQ2) mutations in ubiquinone deficiency and oxidative phosphorylation disorders. J Clin Invest. 2007;117:765-72. PubMed PMID: 17332895.

Montero R, Sánchez-Alcázar JA, Briones P, Hernández AR, Cordero MD, Trevisson E, Salviati L, Pineda M, García-Cazorla A, Navas P, Artuch R. Analysis of coenzyme Q10 in muscle and fibroblasts for the diagnosis of CoQ10 deficiency syndromes. Clin Biochem. 2008;41:697-700. PubMed PMID: 18387363.

Montini G, Malaventura C, Salviati L. Early coenzyme Q10 supplementation in primary coenzyme Q10 deficiency. N Engl J Med. 2008;358:2849-50. PubMed PMID: 18579827.

Nardecchia F, De Giorgi A, Palombo F, Fiorini C, De Negri AM, Carelli V, Caporali L, Leuzzi V. Missense PDSS1 mutations in CoenzymeQ10 synthesis cause optic atrophy and sensorineural deafness. Ann Clin Transl Neurol. 2021;8:247-51. PubMed PMID: 33285023.

Pesini A, Hidalgo-Gutierrez A, Quinzii CM. Mechanisms and therapeutic effects of benzoquinone ring analogs in primary CoQ deficiencies. Antioxidants (Basel). 2022;11:665. PubMed PMID: 35453349.

Rahman S, Clarke CF, Hirano M. The 176th ENMC International Workshop: diagnosis and treatment of coenzyme Q10 deficiency. Neuromuscul Disord. 2012;22:76-86. PubMed PMID: 21723727.

Rötig A, Appelkvist EL, Geromel V, Chretien D, Kadhom N, Edery P, Lebideau M, Dallner G, Munnich A, Ernster L, Rustin P. Quinone-responsive multiple respiratory-chain dysfunction due to widespread coenzyme Q10 deficiency. Lancet. 2000;356:391-5. PubMed PMID: 10972372.

Salviati L, Sacconi S, Murer L, Zacchello G, Franceschini L, Laverda AM, Basso G, Quinzii C, Angelini C, Hirano M, Naini AB, Navas P, DiMauro S, Montini G. Infantile encephalomyopathy and nephropathy with CoQ10 deficiency: a CoQ10-responsive condition. Neurology. 2005;65:606-8. PubMed PMID: 16116126.

Salviati L, Trevisson E, Rodriguez Hernandez MA, Casarin A, Pertegato V, Doimo M, Cassina M, Agosto C, Desbats MA, Sartori G, Sacconi S, Memo L, Zuffardi O, Artuch R, Quinzii C, Dimauro S, Hirano M, Santos-Ocaña C, Navas P. Haploinsufficiency of COQ4 causes coenzyme Q10 deficiency. J Med Genet. 2012;49:187-91. PubMed PMID: 22368301.

Scalais E, Chafai R, Van Coster R, Bindl L, Nuttin C, Panagiotaraki C, Seneca S, Lissens W, Ribes A, Geers C, Smet J, De Meirleir L. Early myoclonic epilepsy, hypertrophic cardiomyopathy and subsequently a nephrotic syndrome in a patient with CoQ10 deficiency caused by mutations in para-hydroxybenzoate-polyprenyl transferase (COQ2). Eur J Paediatr Neurol. 2013;17:625-30. PubMed PMID: 23816342.

Stallworth JY, Blair DR, Slavotinek A, Moore AT, Duncan JL, de Alba Campomanes AG. Retinopathy and optic atrophy in a case of *COQ2*-related primary coenzyme Q_{10} deficiency. Ophthalmic Genet. 2023;44:486-90. PubMed PMID: 36420660.

Terracciano A, Renaldo F, Zanni G, D'Amico A, Pastore A, Barresi S, Valente EM, Piemonte F, Tozzi G, Carrozzo R, Valeriani M, Boldrini R, Mercuri E, Santorelli FM, Bertini E. The use of muscle biopsy in the diagnosis of undefined ataxia with cerebellar atrophy in children. Eur J Paediatr Neurol. 2012;16:248-56. PubMed PMID: 21873089.

Trevisson E, DiMauro S, Navas P, Salviati L. Coenzyme Q deficiency in muscle. Curr Opin Neurol. 2011;24:449-56. PubMed PMID: 21844807.

Wang Y, Hekimi S. Micellization of coenzyme Q by the fungicide caspofungin allows for safe intravenous administration to reach extreme supraphysiological concentrations. Redox Biol. 2020;36:101680. PubMed PMID: 32810741.

Yu MH, Tsang MH, Lai S, Ho MS, Tse DML, Willis B, Kwong AK, Chou YY, Lin SP, Quinzii CM, Hwu WL, Chien YH, Kuo PL, Chan VC, Tsoi C, Chong SC, Rodenburg RJT, Smeitink J, Mak CC, Yeung KS, Fung JL, Lam W, Hui J, Lee NC, Fung CW, Chung BH. Primary coenzyme Q10 deficiency-7: expanded phenotypic spectrum and a founder mutation in southern Chinese. NPJ Genom Med. 2019;4:18. PubMed PMID: 31396399.

Yubero D, Montero R, Armstrong J, Espinós C, Palau F, Santos-Ocaña C, Salviati L, Navas P, Artuch R. Molecular diagnosis of coenzyme Q(10) deficiency. Expert Rev Mol Diagn. 2015;15:1049-59. PubMed PMID: 26144946.

License